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In silico investigation of nanocarbon biosensors for diagnosis of COVID-19

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In this work, advantages of applications of nanocarbon materials were investigated for diagnosis purpose of coronavirus disease 2019 (COVID-19). To do so, interactions of four representative models of nanocarbon materials including carbon nanotube (CNT), carbon nanocone (CNC), carbon graphene (CGR), and carbon fullerene (CFR) were investigated against spike protein (SP) and main protease (MPO) macromolecular targets of coronavirus. The obtained results indicated that the structure of nanocarbon was important to show its functions for complex formation, in which the CNC ligand was seen to strongly interact with both of SP and MPO targets among other nanocarbon ligands. Additionally, CNC showed more flexibility of conformational relaxation against the target through molecular docking simulation processes. As a distinguished achievement of this work, nanocarbon materials could work for diagnosis purpose of COVID-19 with the best function for CNC to achieve the purpose. All results of this work were obtained based on employing the computer-based *in silico* approach at the lowest molecular scale including structural optimization and molecular docking simulation.

KEYWORDS

Nanocarbon; COVID-19; coronavirus; *In silico*; diagnosis.

Introduction

Since the late 2019, the world has been shocked by the threating news of spreading a virus as a global pandemic involving very much serious harmful effects [1]. Very soon after the news, several infected persons have been found almost all around the world, which made sense that bad news very clearly. The virus has been seen to be in the family of severe acute respiratory syndrome-related coronavirus (SARS-CoV) leading to coronavirus disease 2019 (COVID-19) [2]. The speed of pandemic has been very fast and the symptoms of COVID-19 have been seen very soon everywhere, so the governments decided to lock down the cities to put time for developing medical protocols avoiding more spreading of virus and death of infected patients [1]. Many attempts have been dedicated for developing therapeutics for COVID-19, but none of the efforts have been successful yet and considerable numbers of infected persons and victims are announced every day [3-6]. Therefore, the efforts on this topic should be continued non-stop to reach the point of medical diagnosis and therapy for COVID-19. Indeed, early diagnosis or careful diagnosis could detect infected persons not to spread more viruses among other people, so preventing protocol has been seen as the most powerful one against the pandemic up to now,

e.g. wearing a face mask. Additionally, developing diagnosis kits could be very much helpful for such preventing purposes to recognize those infected persons of COVID-19 [7]. To provide such diagnosis kits, smart materials have been seen always as proper candidates for involving in adsorption/desorption process of diagnosis steps [8, 9]. Indeed, biologically related applications of nanostructures have been expected from early days of their introduction by innovating carbon nanotube (CNT) [10]. Very soon after, characteristic features of CNTs were significantly recognized and other nano-related materials were also developed [11-14]. Nanocone, graphene, and fullerene are other examples of nanocarbon materials arising interest of researchers for investigating their characteristic features and applications especially in biological related systems [15-17]. Nanocarbon materials have been used for several applications such as biosensors and drug delivery for biomedical applications. The efforts are still under development [18]. For diagnosis purposes, nanocarbon materials could work very well because of their unique electronic features and wide surfaces enabling them for contributing to molecular interactions [19]. In earlier works, the roles of nanocarbon materials for biosensor applications of early and carful diagnosis of biomarker have been very well investigated [20]. Indeed, complicated biological systems always require systematic investigations to provide insightful information about what happening inside the living systems [21-26]. To this aim, it is important to see the role for nanocarbon materials for diagnosis of biomarkers of COVID-19 to possibly propose a diagnosis kit for such serious harmful pandemic at the global scale.

Within this work, two biomarkers of COVID-19 including spike protein (SP) and main protease (MPO) were targeted to be diagnosed by nanocarbon materials employing *in silico* approach. Both SP and MPO are expressed in the infected people by COVID-19, in which their diagnosis could help for detecting such patients at least for obeying the pandemic prevention protocols [27, 28]. Representative models of nanocarbon materials including CNT, nanocone (CNC), graphene (CGR) and fullerene (CFR) were examined for diagnosis of each of SP and MPO biomarkers. The work was done *in silico* as an advantage of employing computational approaches to solve biomaterial problems and processes at the lowest molecular scale [29, 30]. The interactions between counterparts were assigned by ligand…target interactions, in which each of the nanocarbon materials were located at the ligand position and each of biomarkers were located at the target position to make such interacting ligand…target complexes. The major goal behind this work was to examine the role of nanocarbon materials for possible diagnosis of COVID-19.

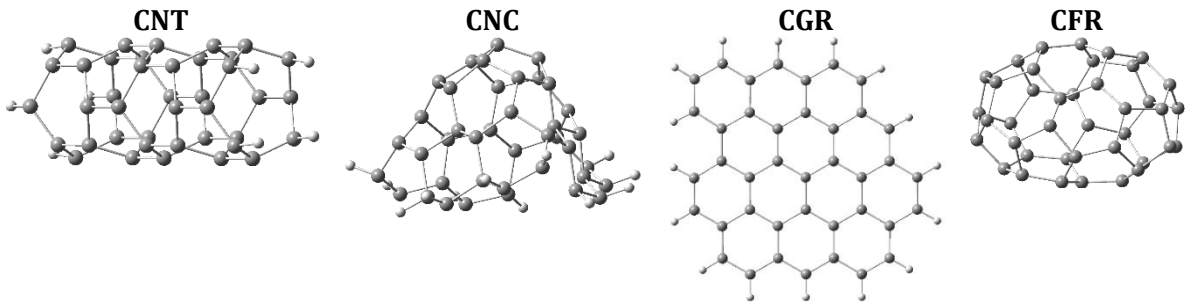

FIGURE 1 Optimized nanocarbon materials

Computational details

This *in silico* work was done by employing 3D molecular models and computational aspects to possibly solve a problem in the case of designing nanocarbon biosensors for COVID-19 diagnosis. Indeed, the computer-based works could always provide insightful information about the investigated systems especially for those of health importance innovations. To this aim, four models of nanocarbon materials including carbon nanotube (CNT), carbon nanocone (CNC), carbon graphene (CGR) and carbon fullerene (CFR) were chosen to play the role of ligand against macromolecules (Figure 1). All ligands were optimized employing the Amber forcefield as implemented in the HyperChem program to reach the minimized energy structures [31]. It is important to note that an acceptable structure of ligand is enough for this work because it should change for several times during the conformational search. By preparation the ligand models, 3D structures of two macromolecules of spike protein (SP 2ghv) and main protease (MPO 6lu7) of coronavirus were obtained from the protein data bank (PDB) and were prepared to play target role of this work [32]. Next, complex formations of ligand…target systems were examined using the molecular docking simulations by AutoDock program [33]. A grid box of 70*70*70 with 1 Å point space was assigned for the complexes to allow ligand freely to relax against target as much as possible. Such conformational relaxation of ligand was done based on genetic algorithm by 50 numbers of search. The results were listed in Tables 1 and 2 and Figures 1-3.

Results and discussion

This work was done to design a possible nanocarbon biosensor for diagnosis of COVID-19. To this aim, four models of nanocarbon materials including CNT, CNC, CGR, and CFR were chosen for the ligand roles to separately interact with each of SP and MPO macromolecules of coronavirus as the target roles (Tables 1 and 2 and Figures 1-3). Recent works indicated that both of SP and MPO could be considered as the targets for drug design against COVID-19 [27,28]. The nanocarbon materials were all including 40 carbon atoms, in which the structures were optimized first to achieve acceptable minimum energy structures. It should be noted that the employed *in silico* procedure of this work was a flexible ligand – fixed target model meaning that the conformation of ligand structure should change several times to find the relaxation position against the fixed target. Therefore, an acceptable 3D molecular model of ligand was enough for the purpose to avoid employing other methods of optimization. By preparing the ligand structures, macromolecular targets were also prepared and the molecular docking simulations were performed to achieve ligand…target complex systems.

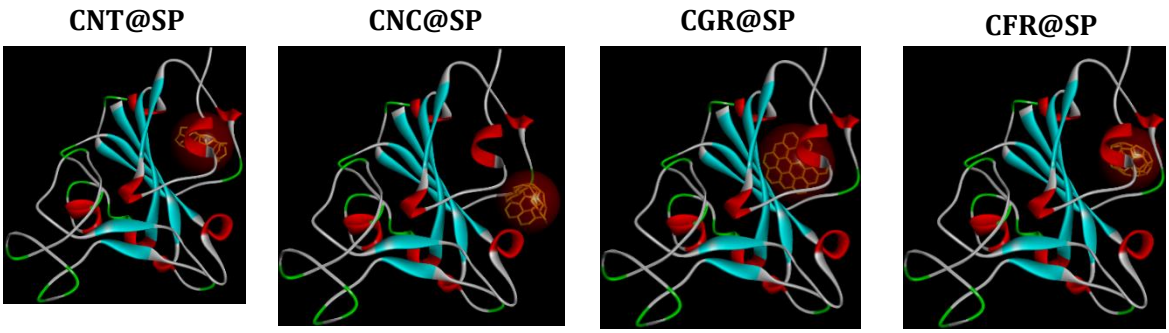

FIGURE 2 Nanocarbon@SP complexes obtained by molecular docking

Nanocarbon@SP complexes

The results of Table 1 and Figure 2 represent the achievements of Nanocarbon@SP complex formations. Four nanocarbon materials including CNT, CNC, CGR, and CFR were investigated in this work for diagnosis purpose of COVID-19. The importance of SP is its coverage role around the coronavirus genome, which could be supposed for better detection of this complex virus. In this case, sensing this SP or catching it with a sensitive material could help the idea of carful detection of this virus to prevent its wide spreading by the infected patients. Each nanocarbon material was separately examined against the SP target to reach to the optimum conformation in the interacting ligand…target complex system. Molecular docking simulations were performed for this purpose to see the quantitative and qualitative features of such interacting systems. A quick look at the panels of Figure 2 could reveal that the ligands preferred to locate in their most favorable position against the target, in which such positions were not identical for all of four carbon nanomaterials. This is an important trend regarding the importance of structural features for assigning a function to the structure, in which different structural nanocarbon materials showed different functions of interactions with target structure. More details of such features were examined by the values of binding energy, in which the order of strength of complex formation could be seen as CNC@SP > CNT@SP > CGR@SP > CFR@SP. The values of inhibition constants also approve the trend of complex strength, in which the lowest concentrations of free ligand and target were seen for CNC@SP and the highest ones were seen for CFR@SP. It is noted that lower concentrations of free ligand and target correspond to higher concentration of ligand…target complex. To this point, CNC could be seen as the most favorable nanocarbon material for interacting with the SP target of coronavirus.

TABLE 1 Molecular docking features of Nanocarbon@SP complexes

Feature	CNT@SP	CNC@SP	CGR@SP	CFR@SP
Binding Energy kcal/mol	-9.17	-9.38	-8.66	-7.53
Inhibition Constant nM	190	133	452	3040
RMSD Å	23.38	44.06	24.76	28.34
Interacting Amino Acids	TYR352	ASN330	TYR352	TYR352
	LEU355	ALA331	THR359	LEU355
	TYR356	THR332	PHE360	TYR356
	ASN357	TYR356	PHE361	ASN357
	SER358	ASN357	PHE364	SER358
	THR359	SER358	LEU377	THR359
	PHE361	THR359	PHE379	PHE360
	PHE364	TRP423		PHE361
	PHE379	ASN424		PHE364
		THR425		
		ASN427		
		ILE428		
		ARG495		

*See Figure 2 for details.

The conical structure of CNC might help it contribute to better interaction with the target, in which values of both of binding energy and inhibition constant approved it. The values of root-mean-square-displacement (RMSD) could show the conformational changes of ligand structures from their initial structure at the starting point of such

ligand…target interaction process up to relaxed system. In this case, CNC showed the most flexibility of undergoing such conformational changes leading to the best localization for ligand against the target to provide the strongest complex formation among other nanocarbon materials. For showing more details of interactions, those interacting amino acids of SP target with the ligands were summarized in Table 1. It could be easily found that the CNC ligand interacted with higher number of amino acids of the SP target, in which the most favorable values of binding energy and inhibition constant were obtained for the CNC@SP complex among other models. Moreover, comparing the types and numbers of amino acids indicated that all of CNT, CGR, and CFR ligands interacted with somehow a common region of the target whereas CNC interacted with a different region. It is noted that the common region of interaction for three mentioned ligands were not completely identical, but could be comparable in the same zone. However, significant discrepancy could be seen for the integration region of CNC. All these achievements could reveal that the SP target could be detected by the nanocarbon materials, in which the CNC ligand could be seen as the best choice for such diagnosis purpose.

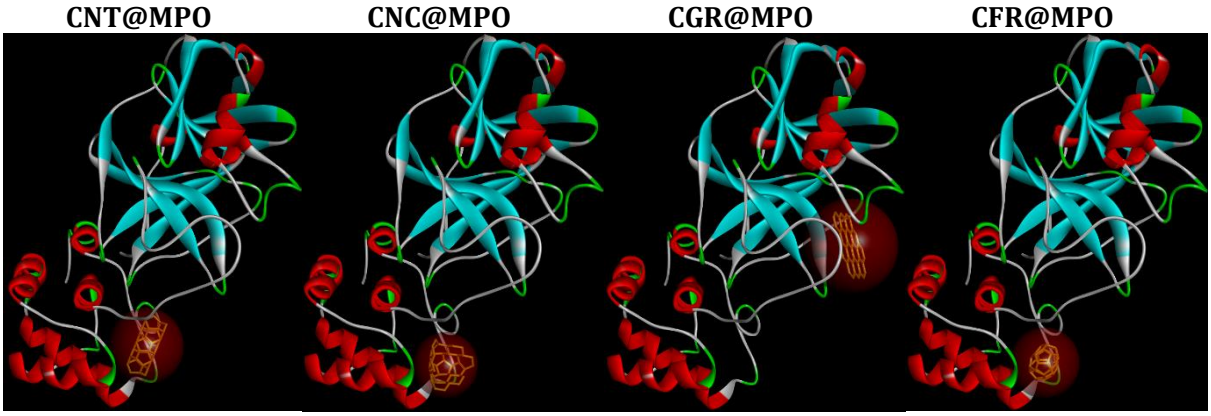

FIGURE 3 Nanocarbon@MPO complexes obtained by molecular docking

Nanocarbon@MPO complexes

In addition to surrounding SP of the coronavirus genome, MPO is also a target of such detection and medication in order to its importance in coronavirus gene expression and replication. Therefore, detection of MPO could be very much helpful for diagnosis and medication purposes of COVID-19. In this work, each of nanocarbon materials were examined against MPO for interacting ligand…target complex formations. The obtained results of this part were summarized in Table 2 and Figure 3. Indeed, this molecular scale study could show details of complicated systems at the lowest possible scale as an advantage of compute-based works [34]. The obtained results could show different conformational relaxation for each ligand against the target MPO to form complexes with different features. In comparison with the earlier discussed Nanocarbon@SP complexes, lower range of changes was seen for the Nanocarbon@MPO complexes regarding their quantitative and qualitative features. The strength of complex formations were arranged with this order CNC@MPO > CGR@MPO > CNT@MPO > CFR@MPO showing the strongest complex for CNC@MPO and the weakest complex for CFR@MPO. This achievement is parallel to earlier achievement on SP complexes to show the CNC ligand as the most favorable one for interacting with the

macromolecular target of COVID-19. As a result, the CNC could be distinguished for the purpose of diagnosis for both of SP and MPO targets. More details of such achievement could be shown by the significant values of inhibition constants and RMSD for the CNC ligand and related complex in comparison with other models. To this point, CNC showed again the most flexibility of conformational changes for localization against the MPO target to reach the strongest ligand…target complex formation. Details of interacting amino acids and also structural representation of Figure 3 could all show such conformational relaxation of ligand against the target molecule, in which CNT, CNC, and CFR located at the common interacting region whereas CGR located at a different region of MPO target. It is important to note that the detection of existence of such SP and MPO macromolecules of COVID-19 could be done by measuring the remaining concentration of nanocarbon in the experimental media. Based on the results, the CNC ligand could be proposed again for the MPO target diagnosis of COVID-19 as an advantage of application of nanocarbon materials for living systems.

TABLE 2 Molecular docking features of Nanocarbon@MPO complexes*

Feature	CNT@MPO	CNC@MPO	CGR@MPO	CFR@MPO
Binding Energy kcal/mol	-8.80	-8.92	-8.81	-8.38
Inhibition Constant nM	356	290	355	725
RMSD Å	50.98	61.96	58.21	58.81
Interacting Amino Acids	ARG131	THR199	HIS41	THR199
	THR199	TYR237	LEU141	TYR237
	TYR237	TYR239	ASN142	TYR239
	TYR239	LEU271	CYS145	LEU271
	LEU271	LEU272	HIS164	LEU272
	LEU272	GLY275	MET165	GLY275
	GLY275	MET276	GLU166	MET276
	LEU286	ALA285	PRO168	ALA285
	LEU287	LEU286	GLN189	LEU286
		LEU287	THR190	LEU287

*See Figure 3 for details.

Conclusion

This *in silico* work was done to examine the application of nanocarbon materials for diagnosis of COVID-19. To this aim, interactions of each of CNT, CNC, CGR, and CFR ligands were investigated separately against each of SP and MPO macromolecular targets. The results indicated the advantage of nanocarbon materials for formation of strong ligand…target complexes, in which the function of each ligand was somehow different for this purpose. In both cases of SP and MPO targets, CNC was seen to work much better than other ligands for complex formation with both targets. Moreover, it showed the most flexibility for conformational relaxation against the macromolecular targets. Details of such achievements indicated the importance of structure for specific function, in which the CNC ligand was proposed for the best function of COVID-19 diagnosis among other investigated nanocarbon materials.

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